ABSTRACT OF THE DISCLOSURE

The present invention provides methods and compositions for detection of compounds that have activity in modulating activity of membrane-spanning, signal-transducing (MSST) proteins, *e.g.*, agonists, and antagonists. The detection method is based upon detection of a conformational change in a MSST protein upon interaction with a ligand. Conformational change of the MSST protein upon ligand interaction is accomplished by modifying the MSST protein to comprise a conformationally sensitive detectable probe, so that ligand interaction that results in a conformational change in the MSST protein is detected by a change in detectable signal from the detectable probe. The conformationally sensitive detectable probe can be a chemical label (*e.g.*, a fluorophore) or moiety integral to the protein (*e.g.*, a protease cleavage site, or immunodetectable moiety). The conformational assays of the invention provide for high-throughput screening.